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14. ABSTRACT
Exposure to pesticides, solvents or traumatic brain injury increase PD risk. This study takes advantage of the population-based PD registry in Santa Clara County, California and extensive state toxicants databases to investigate the causes of PD and PD-related morbidity and mortality. Study Design: Phase 1: The residence history of more than 3,000 PD cases from the population-based PD registry will be linked to geographically-specific exposure information to determine the relationship between toxicant exposure and PD incidence, morbidity and mortality using Cox proportional hazards regression with time-varying measures of chronic exposure, adjusting for confounding. Phase 2: Conduct a case-control study in a stratified random sample of cases and matched controls, collecting information on occupation, traumatic brain injury, and lifestyle risk factor information and conducting exams. Relevance: This work can help identify the causes and, ultimately, ways to prevent PD.

15. SUBJECT TERMS
Parkinson's disease, gene-environment, toxicants, registry, morbidity, mortality, geocode

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Table of Contents

Cover……1

SF 298…….. 2

Table of Contents……3

Introduction……4

Keywords……4

Accomplishments ……..4

Impact …….. 6

Changes/Problems……..6

Products……7

Participants & Other Collaborating Institutions……7

Appendices……...9

1. **INTRODUCTION:**

This proposal investigates the association between Parkinson's disease (PD) risk and residential exposure to environmental toxicants in Santa Clara County, California (SCC). We will leverage our ongoing work that developed the legally-mandated Santa Clara County Parkinson's Disease Registry (SCCPDR) (AB 2248), identifying every SCC resident with PD with funding from USAMRAA W81XWH-07-1-0261 (a TATRC managed NETRP Program). We identified over 2200 PD cases prevalent in 2007, and continue to accrue incident cases. In the current project we will collect lifetime residential histories for PD cases and controls, and will link this data with unique and powerful time- and location-specific toxicant databases developed by the State of California over the past 50 years, in order to estimate cumulative toxicant exposures. We will test hypotheses that PD risk and PD-related morbidity and mortality are greater in persons exposed to pesticides, solvents, PCBs, and air pollutants. In addition, we will conduct a case control study in a stratified random sample of matched case and control subjects in whom we will conduct neurological examinations, collect detailed lifetime risk factor data (including history of traumatic brain injury), collect blood and/or saliva for testing hypotheses of gene-environment interaction and for future hypothesis testing.

2. **KEYWORDS:** Parkinson's disease, gene-environment, toxicants, registry, morbidity, mortality, geocode

3. **ACCOMPLISHMENTS:**

What were the major goals of the project?

YEAR 1: Establish study team; Approvals

- Develop study databases, data security and quality assurance methods (50% complete)
- Convene study investigator team, establish regular team meetings, finalize study protocol (80% complete)
- Train all research staff (60% complete)
- Obtain USAMRMC ORP HRPO approval (Ongoing: detailed description of our progress follows in section below "What was accomplished under these goals?")

YEARS 1-2: Determine if risk of PD is increased in persons exposed to specific environmental toxicants. (has not begun; awaiting USAMRMC ORP HRPO approval)

- Identify all cases of PD in SCC
  - PD case-finding. Continue active surveillance for PD diagnoses using methods developed under USAMRAA W81XWH-07-1-0261.
  - Control subject identification. Controls will be identified from all SCC residents, frequency matched to incident PD cases on age, gender and duration of SCC residence. A sufficient number of controls will be contacted in order to match cases at a 1:1 ratio
  - Determine lifelong residential addresses. a) All subjects will be mailed a questionnaire requesting lifelong address information; b) For non-respondents, we will use a commercial service
  - Determine key covariate information and, for cases, disease features. The mailed questionnaire will include brief, validated self-report questions to collect critical covariate and PD specific information.
  - Geocode addresses using California Environmental Health Tracking Program (CEHTP) expertise
  - Environmental toxicant data. With CEHTP, assess SCC toxicants spatially and temporally using multiple database sources.
  - GIS-Exposure modeling. CEHTP will link residential and toxicant data; cumulative exposures for each subject will be determined.

- Determine if morbidity or mortality is increased in PD cases exposed to environmental toxicants.
  - Death will be determined through annual searches of CA death certificate data obtained through the Vital Statistics Advisory Committee, as well as through searches of the National Death Index
  - Dementia, falls and fall-related morbidity will be determined from review of health utilization records, direct chart abstraction and, as possible, linkage with other CDPH databases

YEARS 2-3: Investigate the role of gene-environment interaction in the risk of PD, morbidity and mortality. (has not begun; awaiting USAMRMC ORP HRPO approval)

- Identify and enroll 200 case and 200 control subjects using stratified random sampling
- Conduct in-person clinical and risk-factor assessments, including history of traumatic brain injury
- Draw blood and extract DNA for genetic analysis
- Analyze DNA for genetic risk variants
- Bank blood for future analyses

YEAR 3: Analysis and Reporting (has not begun)

- Data analysis: toxicant x PD; toxicant x morbidity/mortality; gene-environment interaction
- Prepare results for publication

What was accomplished under these goals?

- The project was transferred to the Northern California Institute for Research and Education at the San Francisco Veterans Affairs Medical Center effective 15 July 2014.
- Develop study databases, data security and quality assurance methods: We have established a preliminary study database. We continue to make modifications to refine the study databases and quality assurance methods. We will continue to modify as needed based on the final protocol approved by USAMRMC ORP HRPO.
- Convene study investigator team, establish regular team meetings, and finalize study protocol: We have established the study investigator team and convened the initial team meeting on 27-Aug-2013. Our internal team meets at frequent intervals. In consultation with experts at our new institution, we are developing approaches that will provide us with the capabilities to most efficiently and rigorously implement the study protocol and achieve study scientific aims. The study protocol will be finalized after review and approval by USAMRMC ORP HRPO.
- Train all research staff: Training of research staff is in progress. We will continue to train as needed based on the final protocol approved by USAMRMC ORP HRPO.
- Obtain USAMRMC ORP HRPO approval:
  Overall Regulatory Status: This study was initially approved by the Committee for the Protection of Human Subjects (CPHS) through the State of California Health and Human Services Agency on 20-June-2011 as a minimal risk study. Because we had not obtained funding, the study was never started and no subjects were enrolled.
    - CHR: After transferring institutions, our IRB of record is the Committee for Human Research (CHR) at the University of California, San Francisco. A submission package to CHR was submitted on 11/10/14. We received pre-review changes back from CHR on 11/20/2014. We made the requested modifications and resubmitted the application to CHR on 12/5/2014. We received a CHR response to our submission package on 2/19/15. We submitted our response to CHR on 2/20/2015. We received CHR approval on 2/26/2015,
    - VA Research and Development Committee (R&DC): After submitting to CHR, our submission was reviewed both by CHR as noted above and also by the VA R&DC. On 1/24/2015 we received a memo from the VA Clinical Workshop Committee outlining the changes being requested by the R&DC. We responded to these changes by submitting

a modification to our protocol on 3/26/2015. Although this annual report is for the period ending 31March2015, we would like to note that we received approval from the VA R&DC on 23April2015.

- o USAMRMC ORP HRPO: We spoke with Ms. Brigit Ciccarello on 17March2015 regarding our regulatory status. We sent Ms. Ciccarello all applicable documents for our HRPO submission on 19March2015. Ms. Ciccarello submitted these documents on our behalf to HRPO on 20March2015. We were assigned an HRPO analyst on 24March2015. We received questions from the HRPO analyst on 31March2015. Although this annual report is for the period ending 31March2015, we would like to note that we responded to these questions on 2April2015.

What opportunities for training and professional development has the project provided?
Nothing to Report.

How were the results disseminated to communities of interest?
Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?
Plans and milestones for the next quarter do not deviate from the original approved SOW.

- We will continue to refine the study database and develop data security and quality assurance methods. We expect that additional modifications to the database will be necessary once we have obtained USAMRMC ORP HRPO approval.
- Continue to convene regular team meetings and continue to train all research staff.
- Finalize the study protocol and data collection instruments.
- Obtain approval from CPHS and USAMRMC ORP HRPO.
- Once we receive approval from USAMRMC ORP HRPO, begin Phase 1 of study

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?
Nothing to Report

What was the impact on other disciplines?
Nothing to Report

What was the impact on technology transfer?
Nothing to Report

What was the impact on society beyond science and technology?
Nothing to Report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change
Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them

The change of institutions and the requirement for review by multiple human subjects review committees resulted in time delays in study initiation. Therefore, the Period of Performance at NCIRE was revised to terminate on March 31st, 2017. As we are still in the process of obtaining USAMRMC

ORP HRPO approval, there will be a delay in beginning any work that involves human subjects (Year 1 and later). There are no other actual or anticipated problems or delays.

Changes that had a significant impact on expenditures

Our expenditures in Year 1 are lower than anticipated due to administrative delays because of changes of Institution. We have not yet begun any human subjects work as we are first must obtain USAMRMC ORP HRPO approval. We have not set up subcontracts with Kaiser and the Public Health Institute as we are awaiting approval first from USAMRMC ORP HRPO so our final protocol is in place. We anticipate that all funds originally requested in Year 1 are still needed to complete our work in future years.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to Report

6. PRODUCTS:
Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Caroline M. Tanner, MD, PhD
Project Role: Principal Investigator
Nearest person month worked: Dr. Tanner has not yet been able to access funds on this project due to administrative procedures associated with the transition of Institutions.
Contribution to Project: Dr. Tanner oversees all aspects of the project study design. She has worked with experts at our new institution to develop approaches that will provide us with the capabilities to most efficiently and rigorously implement the study protocol and achieve study scientific aims. She has overseen the development of study databases, data security and quality assurance methods. She has led team meetings. She has overseen all aspects of the regulatory submissions as detailed above.
Funding Support: W81XWH-13-1-0054

Name: Samuel Goldman, MD, MPH
Project Role: Co-Investigator
Nearest person month worked: 1
Contribution to Project: Dr. Goldman has assisted Dr. Tanner in the oversight of all aspects of the project study design. He has developed study databases, data security and quality assurance methods and worked on all aspects of the regulatory submissions detailed above.
Funding Support: W81XWH-13-1-0054

Name: Kathleen Comyns
Project Role: Project Manager
Nearest person month worked: 2
Contribution to Project: Ms. Comyns has worked under Drs. Tanner and Goldman to assist in the development of study databases, data security and quality assurance methods. She has been assisted in writing study progress reports. She has worked on all aspects of the regulatory submissions detailed above.
Funding Support: W81XWH-13-1-0054

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Since Dr. Tanner's Other Support was last submitted there have been the following changes.

Previously active grants that have closed:

MJFF LRRK2 Cohort Consortium (PI: Schuele)
3/1/2012 – 9/30/2014 0.6 Cal-Months
MJFF: Parkinson's Institute LRRK2 cohort: Clinical and phenotype pre/non-motor and environmental risk assessment
The goal of this proposal is to expand our assessment of existing LRRK2 families by adding new measures and to recruit newly identified LRRK2 families at the Parkinson's Institute, thereby promoting our efforts of clinical genotype-phenotype assessments as well as genotype-environment interactions related to LRRK2 parkinsonism. Role: Co-Investigator

W81XWH-04-1-0490 (PI: Tanner)
4/1/2004 – 5/1/2014 1.0 Cal-Months
DOD: Polychlorinated Biphenyls, Organochlorines, and PD Risk: A Case Control Study in Alaska Natives
The primary goal of this project is to investigate the relationship between polychlorinated biphenyls, organochlorines, other environmental exposures and Parkinson's disease among Alaska Natives.

W81XWH-07-1-0001 (PI: Tanner)
3/1/2007 – 5/1/2014 0.12 Cal-Months
DOD: Registry of Parkinsonism Cases among Alaska Native People living in Alaska
The purpose of this project is to establish a prospective, statewide, population-based Alaska Native Parkinson Registry among Alaska native people living in Alaska.

W81XWH-07-1-0261 (PI: Tanner)
3/1/2007 – 3/31/2013 1.2 Cal-Months
DOD: CA Parkinson's Disease Registry Pilot Project - Coordination Center and Northern CA Ascertainment
The primary goal of this project is to conduct a pilot study for the legally mandated state-wide population based Parkinson's disease registry.

Previously pending grants that are now active:

3R01 ES020718-02S1 ViCTER (PI: Greenamyre)
10/1/2015 – 9/30/2017 2 Cal-Months
MtDNA Damage as a Biomarker for Environmental Mitochondrial Toxicity
The goal of this project is to investigate mitochondrial toxicities from multiple environmental toxicants that have been associated in epidemiology studies with Parkinson's disease (PD). Role: Subproject PI for Tanner project and Subproject Co-Investigator for Goldman project

Michael J. Fox Foundation: (PI: Tanner)
1/1/2014 – 12/31/2014 0.60 Cal-Months
The Parkinson's Progression Markers Initiative Steering Committee Membership
The goal of this steering committee membership is for members to take responsibility for the scientific rationale, study design, site selection, logistics, data management and analysis planning for the PPMI study.

R01 ES017462 (PI: Checkoway)
9/1/2009 – 8/31/2015 0.60 Cal-Months
NIH/NIEHS: Endotoxin Exposure and Risk of Parkinsonism
The goal of this project is to investigate endotoxin exposure as a risk factor for Parkinson's disease and parkinsonism, by investigating a prospective cohort of women textile workers with well-characterized endotoxin exposure information. Role: Co-Investigator

What other organizations were involved as partners?
After we receive approval first from USAMRMC ORP HRPO approval and our final protocol is in place, we will set up subcontracts with Kaiser Permanent Northern California and the Public Health Institute.

9. APPENDICES: None